Selected Musings on Evolving Product Development Issues

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Globalization

- It is here ***now***
- Markets: present and future
- We live in a medical and public health global village
  - Traditional neglected diseases
  - Diseases of development
  - Emerging infectious diseases
- Production: present and future
- Regulatory and Political
- Perceptions and Knowledge
- Competition
  - Human resources, they're not all here!

"Classical" Disparities to Overcome

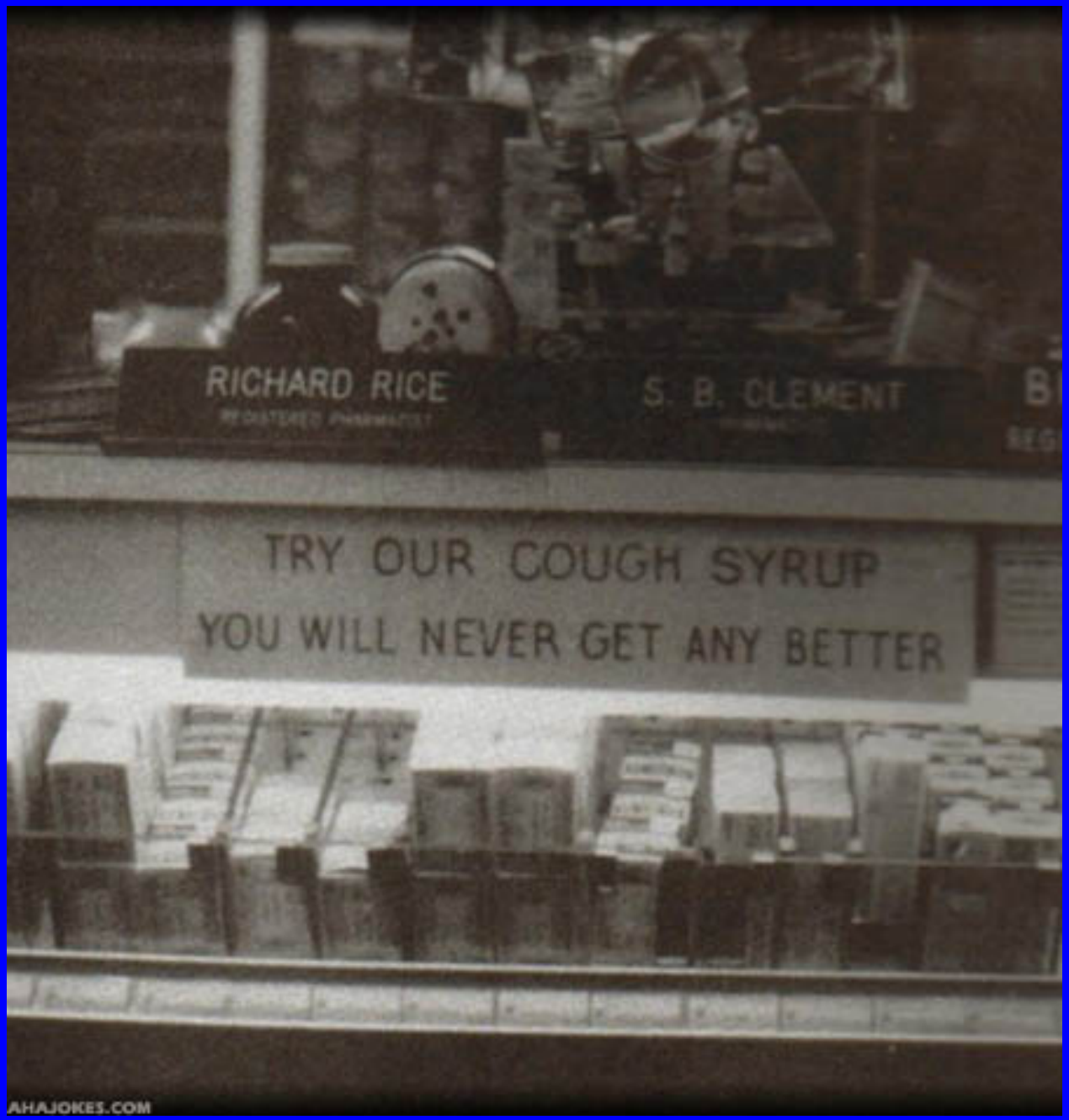
- ***"Africa accounts for 1% of world drug sales, while North America, Japan and Western Europe account for 80%. It is for them the companies invent a stream of high-priced, highly profitable drugs."*** [5]
- **"The 10/90 gap": "Only an estimated 10% of the world's health resources… are used for research into 90% of the world's health problems."** [6]
- ***Sales from a most successful blockbuster drug have exceeded those of all US vaccine industry***
- ***These types of disparities exist within the US as well***
  - *BUT THAT & RESULTANT BUSINESS MODELS MAY BE CHANGING*

McNeil, Jr., DG. NY Times, May 21, 2000 [5]

Ramsey, S. Lancet 358:1348; Oct. 20, 2001 [6]

Public & Individual Health and the Market

- **Public Health and Profits**
  - **Oxymoron? Untapped US and global market?**
  - **What is one product that, if avail., should be received by 6.5 billion people (or 130 million/year)?**
  - **Would it be?**
  - **Unmet needs in CT/emerging infections also teaching lessons & driving policy change (e.g. WNV)**
    - **Public private partnerships**
    - **Acting ahead of the curve and before the market**
  - **Policy makers, health care system and payors seeking documented outcomes and cost-effectiveness**
  - **Health care costs may change support for expensive products/procedures with limited (?define) benefit**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Global Development Challenges for Biological Products

- Ethical issues
- Lack of harmonization
- Manufacturing & clinical trial Capabilities
- Incentives and costs
  - Both to develop and use
- Legitimate Risk-Benefit Differences
- Scientific challenges
  - E.g. Pathogens *and* populations
- Regulatory capacity/responsibility/standards
- First and finally: *it's not just about the products)*
  - Infrastructure and sustainability

Can we reduce costs?

- Increasing challenge to medical product development
- Product development pathway planning ideal
- Use health care systems, informatics, other efficiencies in performing clinical and post-marketing studies
- Don’t collect unneeded data (better not more)
- Well targeted, appropriate size efficacy trial(s)
- Safety trials
  - Scale to product, population and issues
- Large simple trial designs, major endpoints, new technologies in data acquisition and follow-up
- Post-marketing, roll-outs , enhanced data acquisition

How about manufacturing costs?

- Time is money – *reduce time*
- Failure is time – *reduce failure*
- Quality builds success – *invest in quality*
- New technologies
  - Process improvements/measures
  - The right measures (Are they focused on risk? Are they linked to outcome?):
    - Important for FDA activities, too!
  - More rapid tests
  - Non-animal tests
  - More cooperation on common problems
- Can someone else do cheaper, better, faster?
  - Make sure about the “better” part

Not Business as Usual

- Since 9/11, CBER has adapted to extraordinary circumstances through extraordinary efforts
  - These include proactive measures w/ sister agencies and industry such as:
    - **Meetings to encourage developing new products**
    - **Early and intensive interactions w/ sponsors**
    - **Collaboration and rapid turnaround on INDs, EUA**
    - **Proactive trips to inspect facilities**
    - **Participation in multiple product development teams**
    - **Expedited reviews of key product apps.**
  - **Such approaches were used in the 2004 flu season and inform all our activities (for example pandemic preparedness). Benefits and increased demands/stress**

Meeting the Pandemic Flu Challenge: A Paradigm for Global Public Health Preparedness: FDA Steps

- ✓ Increasing manufacturing diversity and capacity
- ✓ Developing needed pathways and regulatory processes to speed vaccine availability
  - ✓ strain change, accelerated approval on immunogenicity
- ✓ Assuring safety and public confidence
- ✓ Facilitating vaccine manufacturing and availability
  - – scientific and related technical needs
  - – enabling both current and evolving technologies
- ✓ Considering pathways to prevent a pandemic
- ✓ Thinking and working globally

Lessons Learned Lead to Other FDA Steps to Strengthen Supply

- Globalization:
  - Information sharing agreements and relationships both completed and being developed - pre and post-licensure
  - Encouraging global vaccine development plans and regulatory cooperation/harmonization
- Annual inspections of flu manufacturers
- GMP initiative – getting down to specifics
  - Increased communications and enhanced preventive approaches including on vaccine GMPs
    - Vaccine roundtable, other meetings focusing on manufacturing- needed guidance/modernization opportunities for industry and FDA

Thinking globally and acting both locally and globally

- Work with public health and industry partners to facilitate building global vaccine capacity – benefits all
- Regulatory and other cooperation to facilitate potential sharing and transnational use of vaccines
- Potential to intervene/vaccinate at geographic site(s) of evolving virulent pandemic strain transmission threat, even prior to widespread human to human spread

Thinking Ahead: Enabling New Approaches and Technologies: Overview

- Even with aggressive and successful efforts to diversify and strengthen US inter-pandemic production, capacity may still be inadequate for true widespread pandemic in US, and, almost certainly, for global needs
- Antigen sparing and other new technologies should be evaluated before a pandemic

Enabling Technology: Scientific Needs

- Addition of adjuvant to vaccine formulation.
  - Results (published and unpublished) in past have been conflicting: adequate studies are needed before adopting
  - Would be considered a new product (requiring BLA)
  - Safety and efficacy (immunogenicity) data required
    - Simplest - aluminum (extensive experience in licensed vaccines)
    - Demonstrate rationale (e.g., *significant* increases in immunogenicity with acceptable safety profile) and determine dose
    - Novel adjuvants or those with previous safety signals would require more safety data
    - Supporting manufacturing and product information needed
  - If proof-of-concept and other studies favorable, Phase 3 studies should be pursued in interpandemic period

Antigen Sparing Strategies

- Changing route of vaccine delivery
  - Simplest change might be i.d. using needle and syringe but raises practicality issues
  - Safety and efficacy (immunogenicity) data needed
  - Other delivery methods promising: need data
- Use of immune stimulators, (e.g. use of patch with heat-labile toxin).
  - Safety and efficacy data required
  - Such strategies are in relatively early development; lack of experience will require safety testing

Enabling New Technologies: Cell Culture & Recombinant Vaccines

- There are significant potential advantages in flexibility afforded by non-egg based technologies
  - Despite problems, egg based manufacturing has been successful & cost effective and, to date, other technologies have not been marketed or widely used
  - FDA has licensed other cell culture derived and recombinant based vaccines and has no special regulatory concerns with these technologies for flu
    - We encourage their development and are providing intensive interactions with sponsors
  - Scientific/technical challenges include:
    - Cell based: usual safety issues (i.e. tumorigenicity, adventitious agents), sufficient yield, manufacturing scale & cost
    - Recombinant or peptide based: antigenicity and protective immune response

Other New Technologies

- Cross-protective antigens
- Live attenuated vaccines
  - Provide multiple immunogens, some may be cross-protective
  - May enhance more rapid development of immunity, avoid multiple dose needs
  - May raise potential containment issues for public health and agriculture

Considering Potential Future Pathways to Preparedness?

- For a pandemic to be a pandemic a prerequisite is the lack of population immunity
- Can we conceptualize pandemic preparedness in a routine prevention rather than crisis mode?
- Should we consider earlier building of immunity against evolving virulent pandemic threat strains?
- Should we consider the potential for integration of such preparedness into routine influenza immunization, as for emerging epidemic strains?
- Transparency, public dialogue, non-crisis environment, are important as we prepare for a pandemic

Unique Regulatory Challenges: the future is now

- Combination products – CBER/CDRH pilots
- Individualized medicine – require new approaches to product controls/clinical trials
- New technology:
  - The right balance of caution and innovation is needed in speeding development
  - New and developing fields high risk from delays, but also from puffed expectations or catastrophic failure
- Urgent availability: CT, EIDs; need vs. risk to confidence in products
- Global regulatory harmonization:
  - Which safety, effectiveness and quality measures?
  - Whose inspections?

Success in Medical Innovation

- All the easy targets are gone, or *more likely the ones we know about right now*
- Don't forget the science but…
  - All the science will not be enough, it also needs to work. You can't wait for *all* the science….
- Fear of failure vs. power of belief (and determination vs. hype) – not a unique business problem!
- If this was easy everyone would do it
  - Then again maybe they are and maybe it isn't
  - The glass is at least half full, or why are we here?
- Leadership: how to support long term results in a short attention span business & political environment?- sometimes *leaders need to be led*

Thank you!

- **We are proud of our staff and our role in public health, biodefense, product safety and availability.**
- **New technologies need innovative and interactive regulation, new models, standards and assays.**
- **Expertise and partnerships essential.**
- **We see a positive future with exciting challenges**
- **We welcome your input.**

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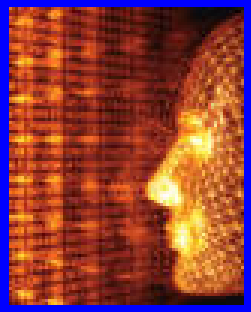
CBER: INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH



Vision for CBER

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

- ***Protect and improve public and individual health in the US and, where feasible, globally***
- ***Facilitate the development, approval and access to safe and effective products and promising new technologies***
- ***Strengthen CBER as a preeminent regulatory organization for biologics***